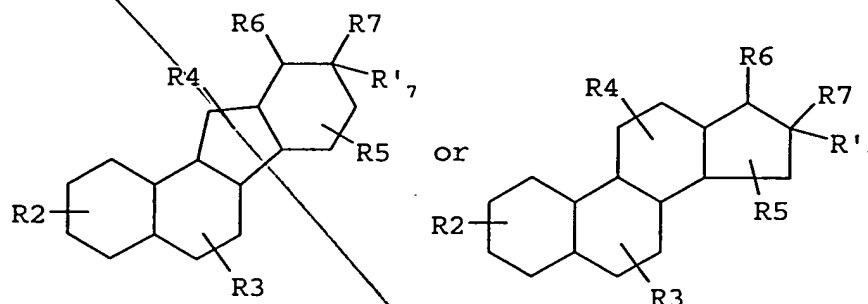


Claims

1. A method for inhibiting paracrine and/or autocrine signals produced by a hedgehog proteins comprising contacting a cell sensitive to the hedgehog protein with a hedgehog antagonist in a sufficient amount to reduce the sensitivity of the cell to the hedgehog protein, wherein the hedgehog antagonist is an organic molecule having a molecule weight less than 750 amu.
2. A method for inhibiting an altered growth state of a cell having a *ptc* loss-of-function phenotype or a smoothened gain-of-function phenotype, comprising contacting the cell with a *ptc* agonist in a sufficient amount to inhibit the altered growth state, wherein the *ptc* agonist is an organic molecule having a molecule weight less than 750 amu.
3. The method of claim 1 or 2, wherein hedgehog antagonist is a the steroidal alkaloid represented in the general formulas (I), or unsaturated forms thereof and/or seco-, nor- or homo-derivatives thereof:

Formula I

wherein, as valence and stability permit,

R_2 , R_3 , R_4 , and R_5 , represent one or more substitutions to the ring to which each is attached, for each occurrence, independently represent hydrogen, halogens, alkyls, alkenyls, alkynyls, aryls, hydroxyl, =O, =S, alkoxyl, silyloxy, amino, nitro, thiol, amines, imines, amides, phosphoryls, phosphonates, phosphines, carbonyls, carboxyls, carboxamides, anhydrides, silyls, ethers, thioethers, alkylsulfonyls, arylsulfonyls, selenoethers, ketones, aldehydes, esters, or $-(CH_2)_m-R_8$;

*See
Fig.
cont.*

~~R₆, R₇, and R'₇, are absent or represent, independently, halogens, alkyls, alkenyls, alkynyls, aryls, hydroxyl, =O, =S, alkoxyl, silyloxy, amino, nitro, thiol, amines, imines, amides, phosphoryls, phosphonates, phosphines, carbonyls, carboxyls, carboxamides, anhydrides, silyls, ethers, thioethers, alkylsulfonyls, arylsulfonyls, selenoethers, ketones, aldehydes, esters, or -(CH₂)_m-R₈, or~~

~~R₆ and R₇, or R₇ and R'₇, taken together form a ring or polycyclic ring, e.g., which is substituted or unsubstituted,~~

~~with the proviso that at least one of R₆, R₇, or R'₇ is present and includes a primary or secondary amine;~~

10 R₈ represents an aryl, a cycloalkyl, a cycloalkenyl, a heterocycle, or a polycycle; and

m is an integer in the range 0 to 8 inclusive.

4. The method of claim 3, wherein:

15 R₂ and R₃, for each occurrence, is an -OH, alkyl, -O-alkyl, -C(O)-alkyl, or -C(O)-R₈;

R₄, for each occurrence, is an absent, or represents -OH, =O, alkyl, -O-alkyl, -C(O)-alkyl, or -C(O)-R₈;

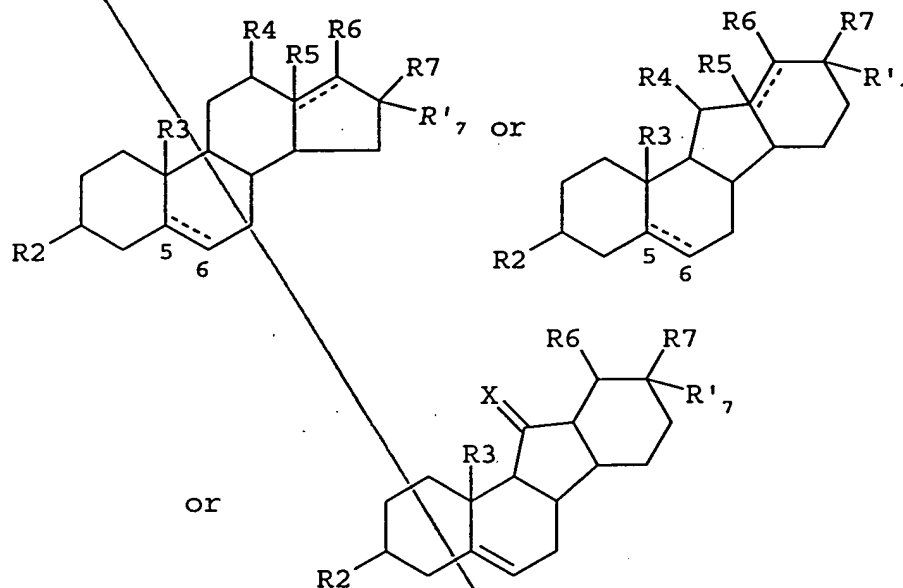
20 R₆, R₇, and R'₇ each independently represent, hydrogen, alkyls, alkenyls, alkynyls, amines, imines, amides, carbonyls, carboxyls, carboxamides, ethers, thioethers, esters, or -(CH₂)_m-R₈, or

R₇, and R'₇ taken together form a furanopiperidine, such as perhydrofuro[3,2-b]pyridine, a pyranopiperidine, a quinoline, an indole, a pyranopyrrole, a naphthyridine, a thiofuranopiperidine, or a thiopyranopiperidine

25 with the proviso that at least one of R₆, R₇, or R'₇ is present and includes a primary or secondary amine;

R_8 represents an aryl, a cycloalkyl, a cycloalkenyl, a heterocycle, or a polycycle, and preferably R_8 is a piperidine, pyrimidine, morpholine, thiomorpholine, pyridazine,

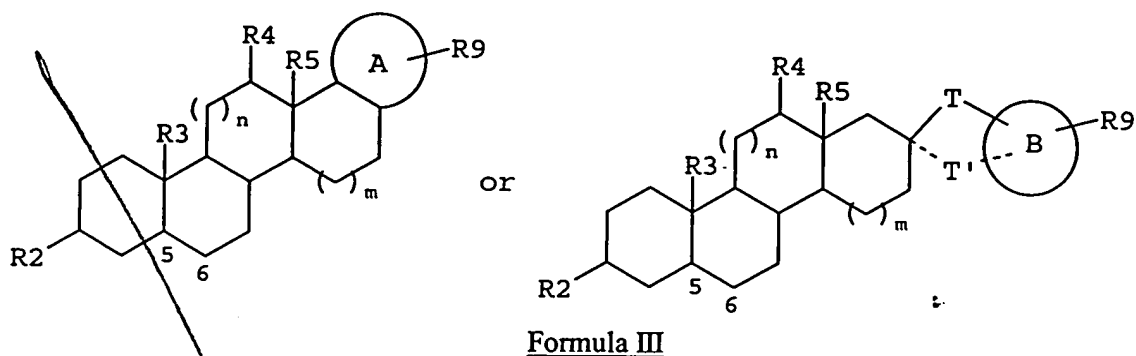
- 5 5. The method of claim 1 or 2, wherein the hedgehog antagonist is a steroidal alkaloid represented in the general formula (II), or unsaturated forms thereof and/or seco-, nor- or homo-derivatives thereof:



Formula II

wherein R_2 , R_3 , R_4 , R_5 , R_6 , R_7 , and R'_7 are as defined above, and X represents O or S, though preferably O.

- 15 6. The method of claim 1 or 2, wherein the steroidal hedgehog antagonist is a alkaloid represented in the general formula (III), or unsaturated forms thereof and/or seco-, nor- or homo-derivatives thereof:



wherein

R_2 , R_3 , R_4 , R_5 and R_8 are as defined above;

A and B represent monocyclic or polycyclic groups;

T represent an alkyl, an aminoalkyl, a carboxyl, an ester, an amide, ether or amine linkage of 1-10 bond lengths;

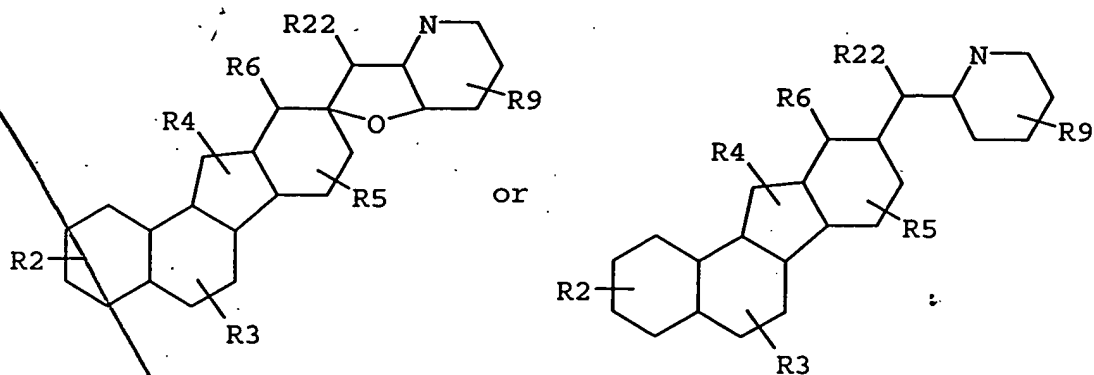
T' is absent, or represents an alkyl, an aminoalkyl, a carboxyl, an ester, an amide, ether or amine linkage of 1-3 bond lengths, wherein if T and T' are present together, than T and T' taken together with the ring A or B form a covalently closed ring of 5-8 ring atoms;

R9 represent one or more substitutions to the ring A or B, which for each occurrence, independently represent halogens, alkyls, alkenyls, alkynyls, aryls, hydroxyl, =O, =S, alkoxy, silyloxy, amino, nitro, thiol, amines, imines, amides, phosphoryls, phosphonates, phosphines, carbonyls, carboxyls, carboxamides, anhydrides, silyls, ethers, thioethers, alkylsulfonyls, arylsulfonyls, selenoethers, ketones, aldehydes, esters, or $-(CH_2)_m-R_8$; and

n and m are, independently, zero, 1 or 2;

with the proviso that A and R9, or T, T' B and R9, taken together include at least one primary or secondary amine.

7. The method of claim 1 or 2, wherein the hedgehog antagonist is a steroidal alkaloid represented in the general formula (IV), or unsaturated forms thereof and/or seco-, nor- or homo-derivatives thereof:

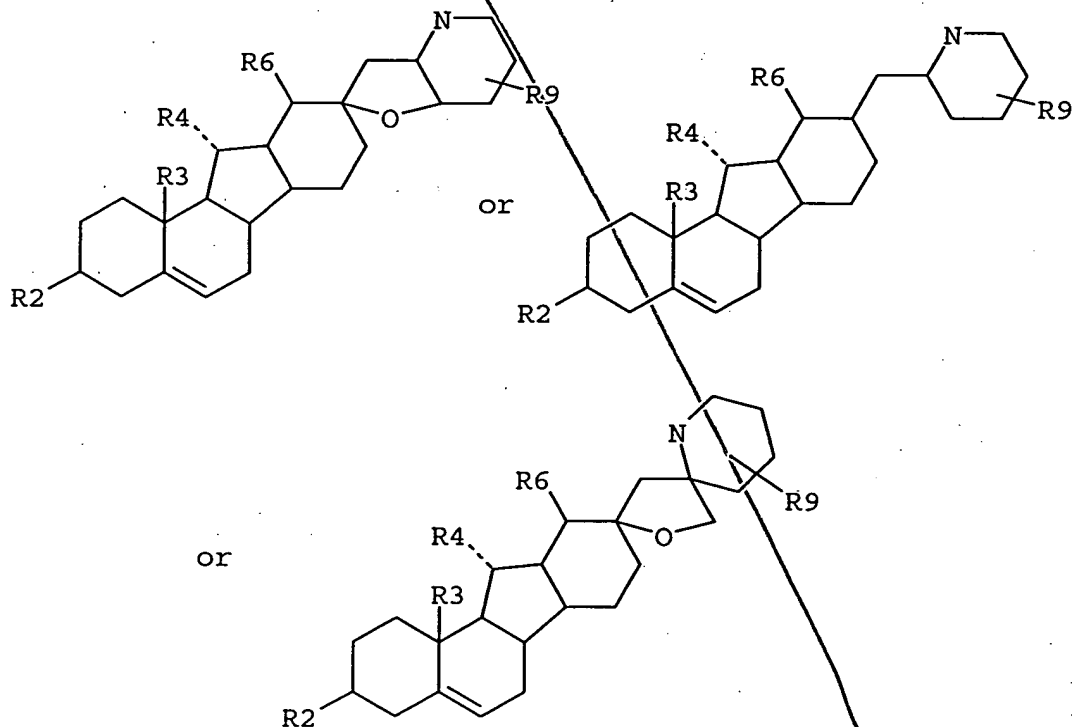
Formula IV

wherein

R₂, R₃, R₄, R₅, R₆ and R₉ are as defined above;

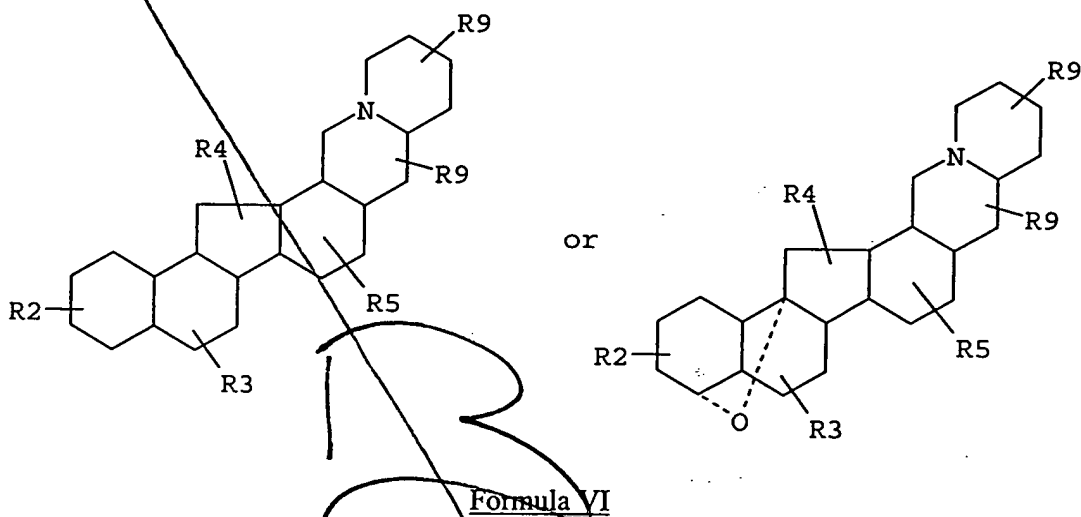
R₂₂ is absent or represents an alkyl, an alkoxyl or -OH.

8. The method of claim 1 or 2, wherein the hedgehog antagonist is a steroidal alkaloid represented in the general formula (V) or unsaturated forms thereof and/or seco-, nor- or homo-derivatives thereof:

Formula V

wherein R_2 , R_3 , R_4 , R_6 and R_9 are as defined above;

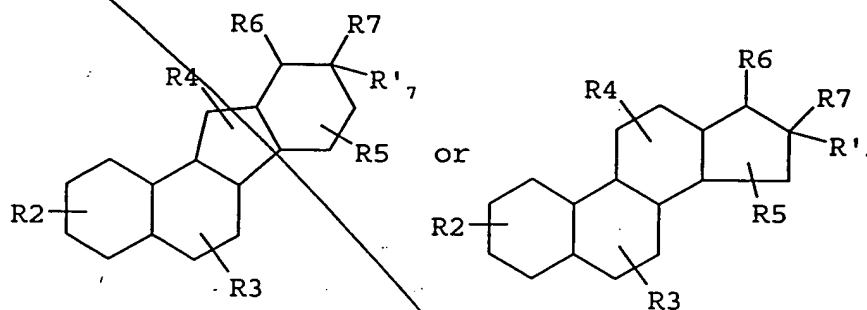
9. The method of claim 1 or 2, wherein the hedgehog antagonist is a steroidal alkaloid represented in the general formula (VI), or unsaturated forms thereof and/or seco-, nor- or homo-derivatives thereof:



- 5 11. The method of any of claims 3-10, wherein the steroidal alkaloid does not substantially interfere with the biological activity of such steroids as aldosterone, androstane, androstene, androstenedione, androsterone, cholecalciferol, cholestane, cholic acid, corticosterone, cortisol, cortisol acetate, cortisone, cortisone acetate, deoxycorticosterone, digitoxigenin, ergocalciferol, ergosterol, estradiol-17- α , estradiol-17- β , estriol, estrane, estrone, hydrocortisone, lanosterol, lithocholic acid, mestranol, β -methasone, prednisone, pregnane, pregnenolone, progesterone, spironolactone, testosterone, triamcinolone and their derivatives.
- 10 12. The method of any of claims 3-10, wherein the steroidal alkaloid does not specifically bind a nuclear hormone receptor.
13. The method of any of claims 3-10, wherein the steroidal alkaloid does not specifically bind estrogen or testosterone receptors.
- 15 14. The method of any of claims 3-10, wherein the steroidal alkaloid has no estrogenic activity at therapeutic concentrations.
15. The method of any of claims 1-10, wherein the hedgehog antagonist inhibits hedgehog-mediated signal transduction with an ED₅₀ of 1mM or less.
16. The method of any of claims 1-10, wherein the hedgehog antagonist inhibits hedgehog-mediated signal transduction with an ED₅₀ of 1 μ M or less.
- 20 17. The method of any of claims 1-10, wherein the steroidal alkaloid inhibit hedgehog-mediated signal transduction with an ED₅₀ of 1nM or less.
18. The method of claims 1 or 2, wherein the cell is contacted with the hedgehog antagonist *in vitro*.
- 25 19. The method of claims 1 or 2, wherein the cell is contacted with the hedgehog antagonist *in vivo*.
20. The method of claim 1 or 2, wherein the hedgehog antagonist is administered as part of a therapeutic or cosmetic application.
21. The method of claim 19 or 20, wherein the hedgehog antagonist is administered to treat a condition selected from the group consisting of regulation of neural tissues,

bone and cartilage formation and repair, regulation of spermatogenesis, regulation of smooth muscle, regulation of lung, liver and other organs arising from the primitive gut, regulation of hematopoietic function, regulation of skin and hair growth, etc.

22. The method of any of claims 1-7, wherein the hedgehog antagonist is applied as a topical formulation to skin in order to inhibit aberrant proliferation of epithelial cells.
23. The method of any of claims 1-7 or 22, wherein the hedgehog antagonist is administered to patient to inhibit growth of a basal cell carcinoma.
24. A pharmaceutical preparation comprising steroidal alkaloid is represented in the general formulas (I), or unsaturated forms thereof and/or seco-, nor- or homo- derivatives thereof:



Formula I

wherein, as valence and stability permit,

R_2 , R_3 , R_4 , and R_5 , represent one or more substitutions to the ring to which each is attached, for each occurrence, independently represent hydrogen, halogens, alkyls, alkenyls, alkynyls, aryls, hydroxyl, =O, =S, alkoxyl, silyloxy, amino, nitro, thiol, amines, imines, amides, phosphoryls, phosphonates, phosphines, carbonyls, carboxyls, carboxamides, anhydrides, silyls, ethers, thioethers, alkylsulfonyls, arylsulfonyls, selenoethers, ketones, aldehydes, esters, or $-(CH_2)_m-R_8$;

R_6 , R_7 , and R'_7 , are absent or represent, independently, halogens, alkyls, alkenyls, alkynyls, aryls, hydroxyl, =O, =S, alkoxyl, silyloxy, amino, nitro, thiol,

Sub
E
cont

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10

~~claim 24, form~~

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